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SHERIDAN ROSS PC 1560 BROADWAY SUITE 1200 DENVER, CO 80202			EXAMINER SHEN, WU CHENG WINSTON	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/500,748

**Applicant(s)**

LEE ET AL.

**Examiner**

WU-CHENG Winston SHEN

**Art Unit**

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 26 March 2008.  
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.  
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-5 and 9-12 is/are pending in the application.  
4a) Of the above claim(s) 1-5 is/are withdrawn from consideration.  
5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.  
6) ☒ Claim(s) 9-12 is/are rejected.  
7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.  
8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.  
10) ☒ The drawing(s) filed on 06/29/2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)  
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)  
3) ☐ Information Disclosure Statement(s) (PTO/5508)  
Paper No(s)/Mail Date \_\_\_\_\_  
4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_  
5) ☐ Notice of Informal Patent Application  
6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

Applicant's response received on 03/26/2008 has been entered. Claims 6-8 and 13 are cancelled. Claims 9-12 are amended and currently under examination.

Claims 1-5 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

This application 10/500,748 is a 371 of PCT/KR01/02304, filed on 12/29/2001

### ***Claim Objections***

1. Claim 9 is objected to because of the following informalities: the limitation "GenBank Accession NO.: AF221517" should read as "GenBank Accession NO.: AF221517". Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

### ***Indefiniteness***

2. Claims 9-12 as amended remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant's arguments filed 03/26/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 3-4 of the office action mailed on 10/26/2007.

*Applicant's Arguments and Response to Applicant's Arguments*

(i) With regard to the nexus between the limitation "homologous recombination" occurring at DNA level and the limitation "to suppress expression of a normal GT protein" at protein level recited in step (b) of amended claim 9, Applicant argues that in the present invention, a vector having a knocked out GT gene is prepared to disrupt the GT gene through the homologous recombination. Therefore, judging based on the third step described in the specification (Construction of a Gene Targeting Vector Carrying a Knocked Out GT Gene and Introduction of the Vector into Nuclear Donor Cells), the phrase "to suppress expression of a normal GT protein" of the present invention obviously refers to knocking out the GT gene through the homologous recombination, and its nexus is clear that the present invention aims to partially knock out the GT gene to suppress the expression of a GT protein rather than the expression of the GT gene by RNAi.

*In response*, in light of Applicant's arguments and the preamble of claim 9 reciting "having an alpha-1, 3,-GT gene knocked out", this aspect of the rejection is *withdrawn*.

(ii) With regard to the recitation of "the method as set forth in claim 6, wherein the gene targeting vector at the step (b) is constructed not to have an exogenous promoter by a *promoter trap method*" in claim 8 being unclear, this aspect of the rejection is *moot* because claim 8 has been cancelled.

(iii) With regard to the recitation of the terms "a wild-type GT gene" and "a normal GT protein" being indefinite, Applicants argues that the term "wild type GT gene" is not unclear, and, further, it may be considered as equivalent to the "GT gene". Thus the amendment from "wild type GT gene" to "GT gene" as disclosed in the specification may be within the scope of permissible amendment. Applicants have amended the claim to recite "a GT protein" by deleting the word "normal", and accordingly, Applicant argues that the amendment fully addresses the problem at issue.

*In response*, the Examiner notes amended claim 9 combines the limitations of cancelled claim 6 and the limitations of previous claim 9. Moreover, the step (b) of amended claim 9 now recites additional limitation "through a PCR method using primers prepared based on a pig GT cDNA sequence (GenBank Accession NO.: AF221517)" (lines 8-9 of amended claim 9). The Examiner acknowledges that the amended claim 9 no longer recites the phrase "a wild type GT gene". However, in contrast to Applicant's arguments, it is noted that the amended claim 9 continues to recite "a normal GT protein" in line 12.

Furthermore, the newly added phrase "through a PCR method using primers prepared based on a pig GT cDNA sequence (GenBank Accession NO.: AF221517)" is unclear for the following reasons: First, GenBank Accession Number is subject to revision with time, in the absence of citation of version and/or date of the recited GenBank Accession Number, the sequences encompassed by the GenBank Accession Number is indefinite. In this regard, Applicant is advised to recite a SEQ ID NO, which is supported by the specification. Second, the phrases "a PCR method" and "a pig GT cDNA sequence" read on "any PCR method" and "any pig GT cDNA sequence". As a PCR method can be used for generation of a library of

mutations (i.e. error-prone PCR) derived from a given pig GT cDNA sequence, the identities of the PCR products are unclear. Based on the two issues discussed above, it is unclear what sequences are encompassed by the limitations that are considered as “GT gene” or “a normal GT protein”. This aspect of the rejection is *maintained*.

Claim 9 is newly rejected for recitation of “wherein the gene targeting vector at the step (b) comprises a nucleic acid sequence *corresponding to* a part of intron 8, exon 9 and a part of intron 9 of a GT gene, wherein an *AvaI*-*DraIII* fragment of said exon 9 is substituted with a nucleic acid sequence encoding a puromycin-resistant gene linked to an SV 40 poly (A) sequence”. The phrase “corresponding to” is unclear because the metes and bounds of the phrase can not be determined. Claims 10-12 depend from claim 9.

Claim 12 recites the limitation “SNU-P2 [Porcine NT Embryo] of claim 9” in the limitation “which is produced from the porcine nuclear transfer embryo “SNU-P2 [Porcine NT Embryo]” of claim 9”. There is insufficient antecedent basis for this limitation in the claim. This rejection is necessitated by claim amendments filed on 03/26/2008.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Previous rejection of claims 9-12 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement as the claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, is *withdrawn* because upon further consideration in light of Applicant's arguments, there is an enabled scope of the claimed, which is documented below. The rejection of claims 6-8 is moot because the claims are cancelled.

#### *Scope of Enablement*

4. Claims 9-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a cloned pig having an alpha-1,3-galactosyltransferase gene knocked out, comprising the steps of: preparing a nuclear donor cell by culturing a *porcine fetal fibroblast cell* (b) isolating an alpha-1,3-galactosyltransferase (GT) gene clone from a *pig genomic library*, and constructing a gene targeting vector using the isolated GT gene, wherein the vector carries a GT gene modified by substituting a portion of a GT gene with a gene encoding a selectable marker by homologous recombination to suppress expression of an *endogenous GT gene*; (c) mixing the vector with a lipid or non-lipid component to form lipid (or non-lipid)-DNA complexes, and adding the resulting complexes to a culture medium of the nuclear donor cell to allow gene targeting by introducing the recombinant GT gene into the nuclear donor cell to produce a transfected nuclear donor cell; (d) transferring the transfected nuclear donor cell with the recombinant GT gene into an enucleated pig recipient oocyte to generate a transgenic nuclear transfer embryo, and activating the nuclear transfer embryo; and (e) transplanting the activated nuclear transfer embryo into a surrogate mother pig to produce live offspring, wherein the gene targeting vector at the step (b) comprises the nucleic

acid sequence of a part of intron 8, exon 9 and a part of intron 9 of a GT gene, *wherein exon 9 comprises an Aval-DraIII fragment*, and wherein the Aval-DraIII fragment of said exon 9 is substituted with a nucleic acid sequence encoding a puromycin-resistant gene linked to an SV 40 poly(A) sequence, **does not** reasonably provide enablement for (1) any porcine somatic cells other than a fetal fibroblast cell, (2) any PCR method used to generate the claimed Aval-DraIII fragment of said exon 9, and (3) any non-viable "SNU-P2 [Porcine NT Embryo]" used for nuclear transfer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The nature of the invention is directed to a method of producing a cloned pig having an alpha-1, 3-galactosyltransferase gene knocked out, comprising a step of preparing a nuclear donor cell by culturing a somatic cell line collected from a pig, and a cloned pig having an alpha-1, 3-galactosyltransferase gene knocked out.

The claims are broadly drawn to (i) use of any cell type as a nuclear donor, and (ii) the cloned pigs with either homozygous or heterozygous knockout of alpha (1,3)-galactosyltransferase (GT) gene.

The specification teaches knockout of pig alpha (1, 3)-galactosyltransferase (GT) gene in the content of heterozygote. However, the specification fails to teach a homozygous knockout, which is necessary to carry out the intended use of the pig, which is as an organ donor allowing xenotransplantation in human without hyperacute immune rejection. The specification discloses gene targeting by introduction of GFP gene into pig fetal fibroblast (Example 4), the selection, proliferation and preservation of nuclear donor cells transfected with GFP (Example 5), and preparation of recipient oocytes (Example 6). However, the specification discloses GT-knockout in the context of heterozygote (See paragraph [0052], US 2005/0076399), and nowhere in the specification discloses a homozygous knockout of pig alpha (1, 3)-galactosyltransferase (GT) gene in the recited cloned pigs. Thus, the specification only provides general guidance for the production of the claimed pigs or method of making a cloned pig to overcome the art recognized unpredictabilities, as more elaboration provided below.

(i) The art of making transgenic animals by somatic cell nuclear transfer was unpredictable at the time of filing. **Clark** et al. teach that only primary somatic cells have been used successfully as a nuclear donor in gene targeting experiments to produce livestock having a

disrupted gene of choice (See page 265, col.2, parag. 1, lines 12-15, Clark et al., Gene targeting in livestock: a preview, *Transgenic Research*, 9:263-275, 2000). In addition, Clark et al. teach that about 45-population doublings are required to generate targeted cells (Clark, page 268, col. 2, parag. 1, lines 1-5). **Denning** et al. teach primary cells have limited proliferation capacity and any genetic modifications and nuclear transfer must be accomplished prior to senescence (See page 222, col. 1, lines 5-8, Denning et al., Gene Targeting from *primary fetal fibroblasts* from sheep and pig, *Cloning and Stem Cells*, 3:221-231, 2001). In a study of sheep and goat primary somatic cells, Denning et al. found that of primary somatic cells, fibroblasts were the only cells that either grew at all from the primary cell source or has sufficient population doublings for the selection required in targeted gene transfer. Sheep primary cell cultures primarily were composed of fibroblasts after the third passage or about 12 doublings (Denning et al., page 224, col. 2, lines 11-13). Further, a comparison of separate Black Welsh sheep primary cell fibroblast cultures showed vast differences in the number of doublings prior to senescence; 110 doublings versus 40 doublings (Denning, page 224, col. 2, lines 16-19). In a similar analysis of pig primary cultures, fibroblasts, as in the sheep study, became the predominant cell-type after three passages, but, unlike sheep, pig fibroblasts underwent a crisis after 40 population doublings and had an unstable karyotype (Denning et al., page 224, col. 2, parag. 4 line 4 to page 225, col. 1, line 8). Additional studies of cell cultures prepare from fetal pig organs (gut, kidney, lung and mesonephros) showed that these cells senesced or entered crisis after even fewer doublings than the fibroblast cultures (Denning et al., page 225, col. 1-2, bridging sentence). The art further taught at the time of filing, that the even if sufficient population doublings could be achieved for selection, many of the pure sheep targeted clones senesced before they could be expanded for

nuclear transfer, meaning that targeting frequency was lower than expected (Denning et al., page 228, col. 1-2, bridg. sent.). Similar experiments in pigs demonstrated that all the clones senesced, and no targeted cells for nuclear transfer were obtained. In experiments for the production sheep comprising a disruption of the alpha-1, 3-galactosyltransferase gene, related to the present claims, live births were achieved but the animals died within two weeks of birth (Denning et al., page 230, col. 1, parag. 2, lines 1-8). However, Denning et al. reports that McCreath achieved live birth and survival of two gene targeted sheep with disruptions in different genes (Denning et al., page 230, col. 1, parag. 2, lines 9-12). Denning et al. analyzed the results of both sheep experiments and arrives at the conclusion that it is possible that for gene targeted sheep, the success depends on unknown factors, whereas in pigs, the use of fibroblasts to produce gene-targeted pigs is not possible (Denning et al., page 230, col.1, parag. 1, lines 7-13). Denning continues to state that for sheep the parameters of cell growth and targeting efficiency reported therein just about make feasible the production of gene targeted sheep. For pigs, Denning et al. continues to state that the lower proliferative capacity indicates that gene targeted pigs are only marginally likely. Further, Given that fibroblasts were the only cells shown to divide a sufficient number of times in sheep to provide cells for nuclear transfer, fibroblasts, derived from the mesoderm, would be the only cell useful for the presently claimed invention (claims 9-12). This is consistent with Applicant's own post-filing publications by **Hyun et al., 2003** (Hyun et al., Production of nuclear transfer-derived piglets using porcine fetal fibroblasts transfected with the enhanced green fluorescent protein. *Biol Reprod.* 69(3): 1060-8, 2003), and **Lee et al., 2005** (Lee et al., Production of transgenic cloned piglets from genetically transformed fetal fibroblasts selected by green fluorescent protein, *Theriogenology*, 63(4): 973-91, 2005)

(ii) Furthermore, claims 9-12 are rejected based on the unpredictability of the presence and location of claimed Aval-DraIII fragment generated by step (b). The specification does not disclose exon 9 sequences, which is asserted to comprise an Aval-Dra III fragment generated by any PCR method encompassed by the limitation of amended step (b).

Amended claim 9 recites, "wherein an Aval-DraIII fragment of said exon 9 is substituted with a nucleic acid sequence encoding a puromycin-resistant gene linked to a SV 40 poly (A) sequence". The Examiner notes that the restriction enzyme site of Aval is C/YCGRG (R: A or G; Y C or T), whereas the restriction enzyme site of DraIII is CACNNN/GTG (N: A or T or G or C). It is noted that the specification discloses neither the size of the claimed Aval-DraIII fragment of said exon 9 nor the nucleotide sequences of exon 9. In fact, the specification does not disclose any sequence information of the asserted isolated pig alpha-l, 3-galactosyltransferase (GT) gene. There is no guidance and/or working example regarding the frequency and locations of Aval and DraIII restriction enzyme sites within a given pig alpha-l, 3-galactosyltransferase (GT) gene. As discussed in the rejection of claims 9-12 under the second paragraph of 35 U.S.C. 112 in this office action, a PCR method can be used for generation of a library of mutations (i.e. error-prone PCR) derived from a given pig GT cDNA sequence. Therefore, it is unpredictable whether an Aval-DraIII fragment is there within exon 9 after any PCR reaction. Moreover, it is known in the art that polymorphisms (including splicing variants) of a GT gene exist among individual organisms of the same species, including claimed GT gene of pigs. Therefore, in the absence of disclosure of critical information of the asserted isolated pig alpha-l, 3-galactosyltransferase (GT) gene in the specification, a skilled

person in the art cannot determine which fragment is the recited "Aval-DraIII fragment of said exon 9" to make and use of the claims 9-12 of instant application.

(iii) In addition to the issues (i) to (iii) discussed above, claims 11 and 12 are also rejected based on the requirements for deposit of biological materials.

The application contains a porcine nuclear transfer embryo "SUN-P2 [porcine NT embryo]" (claims 11 and 12 of instant application), that is encompassed by the definitions for biological material set forth in 37 C.F.R. § 1.801. The specification teaches "SNU-P2 [Porcine NT Embryo]". As "SNU-P2 [Porcine NT Embryo]" is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If "SNU-P2 [Porcine NT Embryo]" is not so obtainable or available, the requirements of 35 U.S.C. 112, regarding "how to make" may be satisfied by a deposit of "SNU-P2 [Porcine NT Embryo]". The specification does not disclose a repeatable process to obtain "SNU-P2 [Porcine NT Embryo]" and it is not apparent if it is readily available to the public. If the deposit is to be made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating "SNU-P2 [Porcine NT Embryo]" has been deposited under the Budapest Treaty and that "SNU-P2 [Porcine NT Embryo]" will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:(a) during the pendency of this

application, access to the invention will be afforded to the Commissioner upon request; (b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent; (c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request of for the effective life of the patent, whichever is longer; and, (d) a test of viability of the biological material at the time of deposit (see 37 CFR 1.807); and, (e) the deposit will be replaced if it should ever become inviable.

In view of the state of the art, the unpredictability in the art, and the lack of specific guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to make and use the claimed invention commensurate in scope with the claims 9-12.

*Applicant's Arguments and Response to Applicant's Arguments*

(i). Applicant states that Applicants have amended the term "a somatic cell line" into the term "a fetal fibroblast cell" to further specify the cell type, and believe that the rejection may be overcome as a result of the amendment (See first paragraph under 35 U.S.C. 112 first Enablement, page 6, Applicant's response filed on 03/26/2008).

*In response:* The amended claim 9 filed on 03/26/2008 continues to recite "a somatic cell line" in step (a). This is in contrast to the statements on page 6 of Applicant's response filed on 03/26/2008. Accordingly, this aspect of rejection remains as a non-enabled embodiment of the scope of enablement rejection in this office action.

(ii). With regard to the rejection based on the absence of disclosure of exon 9 sequences to determine the Aval-Dra III fragment recited in amended claim 9, Applicant argues in Example

3 of the original specification, the GenBank Accession Number of the pig GT gene exon 9 sequence (AF221517) as well as its length are (3.9kb) are described. In addition, the base sequence at which Ava I and DraIII restriction enzyme is operated and cut is well-known, therefore, one of ordinary skill in the art would have easily determined sequences of exon 9 based on the GenBank Accession Number, and according to the sequences, there is only one region where the restriction enzyme, Ava I-DraIII can be operated and cut. Therefore, Applicant argues that even though the sequences of exon 9 are not described, since the region where Ava I-DraIII restriction enzyme of exon 9 can be operated is clear, the sequences of the fragment are clear as well.

*In response:* The newly added phrase "through a PCR method using primers prepared based on a pig GT cDNA sequence (GenBank Accession NO.: AF221517)" reads on "any PCR method" and "any pig GT cDNA sequence". As a PCR method can be used for generation of a library of mutations (i.e. error-prone PCR) derived from a given pig GT cDNA sequence set forth in GenBank Accession NO.: AF221517, it is unpredictable whether a PCR product derived from the sequence set forth in GenBank Accession NO.: AF221517 comprises the claimed "an Aval-Dra III fragment" recited in claim 9. Furthermore, the sequences of the recited GenBank Accession No. are subjected to changes with time. Therefore, this aspect of rejection remains as a non-enabled embodiment of the scope of enablement rejection in this office action.

(iii). With regard to the rejection of claims 11 and 12 is based on the rejection of claim 11 and 12 is based on the requirements for deposit of biological materials, Applicant argues that every necessary matter for implementing the present invention is described in detail through exemplary embodiments. Applicant states that claim 11 is described in Examples 1 to 4 and 6 to

9 in the specification; and in the Argument in response to the Office Action, the scope of the claims is further specified to easily embody the claimed invention based on the exemplary embodiments. Furthermore, Applicant states that claim 12 is described in Examples 12 to 14 in the specification, and thus the exemplary embodiments are sufficient to enable one of ordinary skill in the art to easily embody the claimed invention. Moreover, the amendment filed in response to the Office Action further narrows the scope of Claim 12, and thus the exemplary embodiments are sufficient to enable one of ordinary skill in the art to embody the claimed invention.

*In response*, as elaborated in the scope of enablement of this office action, this aspect of rejection remains as a non-enabled embodiment of the claimed invention.

***Written description***

5. Previous rejection of claims 9-12 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is *withdrawn* because Applicant's arguments in light of claim amendments have been fully considered and found persuasive.

With regard to whether Applicant at the time the application was filed, had possession of the claimed invention with respect to "a GT gene" recited in step (b) of claimed method, Applicant argues that claim 6 has been cancelled and claim 9 has been amended to recite "isolating an alpha-1,3-galactosyltransferase (GT) gene clone from a pig genomic BAC library

through a polymerase chain reaction (PCR) using primers prepared based on a pig GT cDNA sequence (GenBank Accession No.: AF221517)".

Applicant agrees with Applicant's arguments that "a GT" gene" can be generated by PCR. Accordingly, one skilled in the relevant art that the inventor(s), at the time the application was filed would recognize that the Applicant had possession of the claimed GT gene. It is noted that whether the claimed GT gene is enabled has been addressed separately.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claim 9 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Day et al.** (US publication NO 2005/0120400, publication date, 06/02/2005, effective filing date 12/21/2001) in view of **Mason et al.** (US patent 5,576,201, issued 11/19/1996).

*Claim interpretation:* The limitation of step (b) of claim 9 recites "isolating an alpha-1,3-galactosyltransferase (GT) gene clone from a pig genomic BAC library through a PCR method using primers prepared based on a pig GT cDNA sequence (GenBank Accession No.: AF221517). This limitation is interpreted as a "product by process" (i.e., that the gene clone is produced by a different method would still have the same structural and functional limitations)

because isolating the gene clone from the BAC library does not impart patentable weight as it does not impart a difference in the gene clone for knockout purpose.

Day et al. teaches viable gene knockout swine including swine in which the alpha (1, 3)-galactosyltransferase gene has been disrupted; methods for making such swine (See abstract, Figure 3, Day et al., 2005).

With regard to step (a), Day et al. teaches that the donor cell is a primary fibroblast (See paragraph [0030], Example 1, Day et al., 2005).

With regard to step (b), Day et al. teaches GalGT targeting vector and genomic PCR assays for targeting. The structure of the region of the alpha (1, 3)-galactosyltransferase (GGTA1) locus beginning with exon 7 is depicted (scale in kilobase pairs). GGTA1 homologous sequences in the pGalGT vector begin .about.0.8 kb downstream of exon 7 and continue to about 6.8 kb downstream of the end of exon 9. A selection cassette, consisting of a Bip internal ribosome entry site, APRT coding sequences (encoding G418 resistance) and flanking stop codons, is inserted into an Eco RV site upstream of the GGTA1 catalytic domain in exon 9 (See Figure 1, Day et al., 2005).

With regard to step (c), Day et al. teaches that approximately  $2 \times 10^7$  fibroblasts were electroporated at 260 V, 960 uFD in 0.8 ml of Hepes buffered saline containing 0.5 pmol/ml of pGalGT. The vector was restriction digested at both ends of the GGTA1 homologous sequences prior to use. Transfected cells were cultured in bulk for 2 days without selection, then plated in collagen-coated 96 well plates at  $2 \times 10^4$  cells per well in Ham's nutrient mixture F10-20% fetal bovine serum (FBS) containing 100 µg/ml G418 (See paragraph [0061], Day et

al., 2005). These disclosures by Day et al. teach “mixing the vector with non-lipid component to form non-lipid-DNA complexes and adding the complexes to a culture medium of nuclear donor cell” recited in step (c) of claim 9 of instant application.

With regard to step (d), Day et al. teaches the nuclear transfer of transfected donor fibroblast cells into enucleated oocytes (See Example 2, paragraph [0066], Day et al., 2005).

With regard to step (e), Day et al. teaches transplantation of nuclear transfer (NT)-derived embryos to mated surrogates (See Example 3, paragraph [0066]-[0070], Day et al., 2005), and transplantation of nuclear transfer (NT)-derived embryos to unmated surrogates (See Example 4, paragraph [0071], Day et al., 2005).

With regard to claim 12, the claim is a product-by-process claim reciting the cloned pig is produced from the porcine nuclear transfer embryo "SUN-P2 [Porcine NT Embryo]" of claim 9 performing the method at step (c) of claim 9. In this regard, Day et al. teaches viable gene knockout swine including swine in which the alpha (1, 3)-galactosyltransferase gene has been disrupted; methods for making such swine (See abstract, Figure 3, Day et al., 2005). Since the cloned pigs are claimed as product-by-process, applicant bears the burden to provide evidence that distinguishes the claimed products over those known in the prior art at the time of filing.

[E]ven though product-by-process claims are limited by and defined by the process; determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.” In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

“The Patent Office bears a lesser burden of proof in making out a case of *prima facie*

obviousness for product-by-process claims because of their peculiar nature” than when a product is claimed in the conventional fashion. In *re Fessmann*, 489 F.2d 742, 744, 180 USPQ 324, 326 (CCPA 1974). Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. In *re Marosi*, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983).

“Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product (*In re Ludtke*). Whether the rejection is based on “inherency” under 35 USC 102, on “prima facie obviousness” under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO’s inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).”

“When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.” *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), *In re Ludtke*, 441 F.2d 660, 169 USPQ 563 (CCPA 1971), *Northam Warren Corp. v. D. F. Newfield Co.*, 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934.) See MPEP 2113 and MPEP 2112.01.

However, Day et al. does not teach a vector with puromycin-resistant gene linked to an SV40 poly (A) sequences recited in step (e) of claim 9 of instant application.

**Mason et al.** teaches a transducing vector with puromycin-resistant gene linked to a SV40 poly (A) sequences (See Figure 3, Mason et al., 1996).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Day et al. and Mason et al. to arrive at the claimed method of producing a cloned pig having an alpha (1,3)-galactosyltransferase gene knocked out.

One having ordinary skill in the art would have been motivated to combine the teachings of Day et al. and Mason et al. because both puromycin and G418 are commonly used selection marker used for select cells that have been transfected with target DNA vector, and SV40 poly (A) sequences is commonly used in a vector for proper expression of cloned gene of interest.

There would have been a reasonable expectation of success given (i) successful generation of a cloned pig which the alpha (1,3)-galactosyltransferase gene has been disrupted, (ii) demonstration of transducing vector that harbors puromycin-resistant gene linked to an SV40 poly(A) sequences. The ordinarily skilled artisan would be well-versed and knowledgeable in various vectors that could be used in transfecting cells, because these techniques would be well within the skills of the ordinary artisan.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

7. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Day et al.** (US patent publication 2005/0120400, publication date, 06/02/2005, effective filing date 12/21/2001) in view of **Mason et al.** (US patent 5,576,201, issued 11/19/1996) as applied to claim 9 above,

and further in view of **Zhao et al.** (US patent publication 2003/0092070, publication date, 05/15/2003, effective filing date 08/30/2001).

The teachings of Day et al. and Mason et al. have been discussed in the preceding section of the rejection of claim 9 under 35 U.S.C. 103(a) as being unpatentable over Day et al. (US publication NO 2005/0120400, publication date, 06/02/2005, effective filing date 12/21/2001) in view of Mason et al. (US patent 5,576,201, issued 11/19/1996).

Neither Day et al. nor Mason et al. teaches FuGENE6 used for transfection as recited in claim 10.

**Zhao et al.** teaches DNA was transfected into each well using Fugene6 (Roche) following manufacture's protocol (See paragraph [0100], Zhao et al., 2003).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Zhao et al. on the use of FuGENE6 for transfection, into the combined teachings of Day et al. and Mason et al. directing to a method of generation of a cloned pig which the alpha (1, 3)-galactosyltransferase to arrive at claim 10 of instant application.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Zhao et al. into the combined teachings of Day et al. and Mason et al. because FuGENE6 is commonly used to enhance the DNA transfection efficiency.

There would have been a reasonable expectation of success given (i) successful demonstration of a method of generation of a cloned pig which the alpha (1,3)-galactosyltransferase by combined teachings of Day et al. and Mason et al., (ii) successful demonstration of enhanced DNA transfection into Hela cells by the teachings of Zhao et al. It is

further noted that utilizing various transfection reagents, such as FuGENE6 would be well-  
within the capabilities of the ordinarily skilled artisan.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

### ***Conclusion***

8. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

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